REMARKS

Claims 1, 3-18, and 21-25 are pending. Claims 26-29 have been added. Applicants reserve the right to pursue any canceled subject matter in one or more continuation, divisional, or continuation-in-part applications.

Support for Amendments

Claims 17 and 18 have been amended. Support for this amendment can be found in, *e.g.,* table 1 and paragraph 50 of the application as published.

New claims 26-29 are added as various embodiments of the invention. Support can be found in, *e.g.*, paragraphs 25 and 30, and claims 8 and 15 of the application as published.

No new matter is entered.

Rejection Under 35 U.S.C. § 103(a)

Claims 1, 3-18 and 21-25 are rejected under 35 U.S.C. § 103 as being unpatentable over Bowman et al. (WO 00/69441, published November 23, 2000) in view of Ishikawa et al. (Biochemical Pharmacology, 1998, vol. 55, pages 1091-1097). The Office Action argues that it would have been obvious to use capecitabine in combination with ET-743 according to the teachings of Bowman in view of Ishikawa, and that "[s]election of appropriate dosage regimens will vary according to the particular formulation, mode of applicant, and the particular *situs*, host and tumor being treated, and such selection would have been well within the purview of the skilled artisan" (Office Action, page 4). In response to Applicants' arguments filed on February 4, 2008, the Final Office Action asserts that "use of materials in combination, each of which is known to function for intended purpose, is generally held to be prima facie obvious as the idea of combining them flows logically from their having been individually taught

in the prior art" and that "Bowman clearly suggests using ET743 in combination with other drugs for cancer treatment" and "Ishikawa explicitly teaches the preference for using capecitabine over 5-fluorouracil" (Office Action, page 5). Applicants respectfully traverse the rejection.

U.S. case law holds that a proper obviousness inquiry requires four factual inquiries: (a) determining the scope and contents of the prior art; (b) ascertaining the differences between the prior art and the claims in issue; (c) resolving the level of ordinary skill in the pertinent art; and (d) evaluating evidence of secondary consideration. See *Graham v. John Deere*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). Although the Supreme Court in KSR recently rejected a rigid application of the "teaching, suggestion, motivation" test, the Court did recognize that a showing of "teaching, suggestion, or motivation " to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a). See *KSR Int'l Co. v. Teleflex, Inc.*, No 04-1350 at 15 (U.S. Apr. 30, 2007). The Court further noted that an analysis supporting a rejection under 35 U.S.C. § 103(a) should be made explicit, and that "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR*, slip op. at 14.

Therefore, Applicants respectfully traverse the rejection on the basis that 1) the references fail to teach all of the claimed elements, and 2) the references fail to provide a reason for one of ordinary skill in the art to arrive at the claimed elements. These factors provide a helpful insight in determining obviousness, and in view of these factors, the claims are not obvious under 35 U.S.C. § 103(a) from the combination of cited references.

The invention that is the subject of the present application shows for the first time that a combination of ET-743 and capecitabine can be administered to humans with significant therapeutic efficacy and manageable toxicity. Applicants respectfully submit that this was not obvious with regards to the prior art.

As disclosed in Ishikawa, at the time that the invention was made, it was known that capecitabine was a prodrug of 5-FU that is converted to 5-FU primarily in tumor tissues, thus a better tolerability is expected, and this also offers the convenience of oral administration. However, Applicants submit that not all the combinations of an antitumoral drug with capecitabine are necessarily going to have acceptable tolerability in human patients. As evidence thereof, we provide herewith an example of an antitumoral drug which had prior demonstrated synergistic cytotoxic activity in combination with 5-FU *in vitro,* but, when the combination between said antitumoral and capecitabine was assayed in a Phase I clinical trial, the combination showed no manageable toxicity and minimal antitumoral activity.

9-Nitrocamptothecin (9-NC) is an orally available camptothecin analog. In preclinical studies on cultured tumor cells, the combination of 9-NC with other chemotherapeutic agents, including 5-FU, gemtabicine and paclitaxel was examined (Bernaki et al., Ann NY Acad Sci. 2000; 922:293-297; "In vitro antitumor activity of 9-nitro-camptothecin as a single agent and in combination with other antitumor drugs"). Concurrent combination of 9-NC with 5-FU, gemcitabine or paclitaxel suggested that the most synergistic drug combination against human HCT-8 colon cancer cells was 9-NC with 5-FU. In addition, sequential combination of 9-NC followed by 5-FU, 24h later, appeared to be the most synergistic at high growth inhibitory levels.

The combination of 5-FU with camptothecin was also well established in Phase III studies.

A Phase I dose-escalation study was designed to evaluate the safety and tolerability of the oral combination of 9-NC with capecitabine (Michaelson et al, Cancer, 2003 Jan 1; 97(1): 148-154; "A Phase I study of 9-nitrocamptothecin given concurrently with capecitabine in patients with refractory, metastatic solid tumors"). The rationale for combining capecitabine and 9-NC was to recapitulate the synergism between 5-FU and camptothecin in an oral regimen and it was expected that major toxicities would be ameliorated with this oral regime. Some studies have prior shown that capecitabine induced less nausea compared with intravenous 5-FU. Although nausea and emesis were excluded as dose-limiting toxicities (DLT's) in the initial design, in practice, investigators noted that, despite aggressive antiemetic prophylaxis, nausea and emesis were the DLT's and consequently an official amendment was made. In conclusion, although a better tolerability was expected with regards to 5-FU, the combination of 9-NC with capecitabine showed no manageable toxicity and a minimal clinical efficacy; the study's author's noted that "the lack of any objective responses was disappointing, particularly considering the toxicity of this schedule."

Therefore, Applicants respectfully submit that, contrary to the Office Action's assertion, although it was described in Bowman that ET-743 may be used with other drugs to provide a combination therapy and suitable candidates include antimetabolite drugs such as 5-fluorouracil; and it was known that capecitabine is a 5-fluorouracil prodrug, it would not have been obvious to a person of ordinary skill at the time the invention was made that the combination of ET-743 with capecitabine would be "tolerable and feasible, with evidence of antitumor activity" (paragraph 16 of the application as published) when administered to human patients. For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this rejection.

CONCLUSION

Based on the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **50-3732**, Order No. 13566.105023. In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **50-3732**, Order No. 13566.105023.

Respectfully submitted,
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